Diffuse idiopathic skeletal hyperostosis in smokers is associated with Restrictive Spirometry Pattern: an analysis in the COPDGene cohort

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Conflict of interest:

In the past three years, Edwin K. Silverman received honoraria from Novartis for Continuing Medical Education Seminars and grant and travel support from GlaxoSmithKline.

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ABSTRACT (word count=248)

Objective

Diffuse idiopathic skeletal hyperostosis (DISH) is a condition characterized by bony proliferation at sites of tendinous and ligamentous insertions in the spine. Spinal mobility is reduced in DISH and may affect movement in the thorax, potentially leading to restrictive pulmonary function. This study investigated whether DISH is associated with restrictive spirometry pattern (RSP) in former and current smokers.

Methods

1,784 participants with complete post-bronchodilator spirometry who did not meet spirometric criteria for COPD at time of enrollment in the COPDGene study were included in this study. Subjects were classified as RSP if they had Forced Expiratory volume in one second \(FEV_1) to Forced Vital Capacity (FVC) ratio > 0.7 with an FVC<80%. CT scans were scored for the presence of DISH in accordance with the Resnick criteria. Chest CT measures of interstitial and alveolar lung disease, clinical symptoms, health surveys, and six-minute walking distance (6MWD) were recorded. Uni- and multivariable analyses were performed to test the association of DISH with RSP.

Results

DISH was present in 236 subjects (13.2%). RSP was twice as common in participants with DISH (N=90/236, 38.1%) compared to those without DISH (N=301/1548, 19.4%), p<0.001. In multivariable analysis DISH was significantly associated with RSP (OR 1.78; 95%CI; 1.22-2.60; p=0.003) after adjusting for potential confounders. The RSP group with and without DISH had significantly worse spirometry, dyspnea, SGRQ score, BODE and SF-36.

Conclusions

In heavy smokers with an FEV1/FVC ratio > 0.70, DISH is associated with RSP after adjustment for intrinsic and extrinsic causes of restrictive lung function.

Clinical trial registration number: NCT00608764

Key words: diffuse idiopathic skeletal hyperostosis, computed tomography, spirometry, lung function

Key messages:

- DISH is characterized by bony proliferation at tendinous and ligamentous insertions of the spine.
- DISH is associated with a reduced pulmonary function in former and current smokers.
- DISH maybe more than an innocent incidental imaging finding.

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is a common condition characterized by bony proliferation at sites of tendinous and ligamentous insertion of the spine. On imaging, it is typically characterized by flowing ossification in the area of the anterior longitudinal ligament most commonly in the thoracic and lumbar spine and in some cases may be associated with extraspinal enthesopathies [1]. DISH is a disease of aging with increasing prevalence with advancing age especially prominent in the 6th to 7th decade. The estimated prevalence is around 10% with a male predominance [2]. The condition is commonly identified as an incidental finding when imaging is performed for other reasons [3]. However, spinal stiffness and decreased mobility are described as possible symptoms. The etiology of DISH is still unknown, but it is associated with diabetes mellitus type II and obesity [4]. The bridging osseous tissue between vertebral bodies in DISH creates a stiff 'thoracic cage' that may affect ventilation [5]. More recently it has been shown that DISH is associated with lower lung volumes (CT measured Lung Capacity) [6]. A limitation of that study was that for the functional assessment only pre- bronchodilator spirometric data was obtained. Furthermore, kyphotic angle, which may be associated with pulmonary restriction, was not available in that cohort.

Restrictive spirometric pattern (RSP) in general population studies, can be explained by intrinsic or extrinsic restrictive factors. The intrinsic group of factors can be divided into interstitial, pleural and alveolar disease processes. Known extrinsic factors are obesity, abdominal ascites, neuromuscular diseases and kyphoscoliosis [7]. While measurement of lung volumes is required to define a true restriction, in 1991 the American Thoracic Society suggested that a restrictive ventilatory defect defined as abnormally low FVC in combination with a normal or high FEV1/FVC ratio could be termed a ‘’restrictive pattern” [8]. Previous work in the COPDGene study has shown that many heavy smokers with normal FEV1/FVC ratio and reduced FEV1(<80%predicted) can be classified as PRISm, a category distinct from the GOLD classification for COPD that also has characteristics suggestive of restriction and distinct from RSP [9,10]. The PRISm

group of smokers had increased prevalence of diabetes, central obesity, greater mortality, more respiratory symptoms, less emphysema and more airway wall thickening. Based on these definitions RSP is a subset of both "normal" spirometry and PRISm groups. COPDGene is a unique cohort in that it included subjects with a heavy smoking history and excluded subjects with previously diagnosed interstitial lung disease (ILD) or significant ILD identified on chest CT. The selection bias in the design of the COPDGene cohort suggests that many subjects in this cohort will be dominated by risk for COPD progression rather than classic "restriction."

We hypothesized that DISH in heavy smokers with no known ILD would have a higher incidence in subjects with RSP compared to those with "normal" physiology and that this association would be independent of known other factors for restriction. Our aim was to investigate the relationship between DISH and RSP in current and former smokers with an FEV1/FVC ratio > 0.70 who were participating in the COPDGene study.

Methods

Subjects

All subjects in this report were participants in the COPDGene study (ClinicalTrials.gov Identifier NCT000608764) and enrolment and exclusion criteria have been previously described [13]. In short, the COPDGene study was initiated in 2007-2011 enrolling 10,192 smokers with a minimum of 10 pack years smoking and 108 never smokers (non-Hispanic white and African-American), with the goal to define subtypes of smoking-related lung disease and genetic associations to those subtypes. Chest CT scans were performed and extensive clinical data has been obtained. All subjects provided written informed consent, and the study was approved at each of the 21 clinical centers. COPDGene specifically excluded

those with a diagnosis of interstitial lung disease (ILD) and other lung diseases (except a history of asthma) and additionally excluded subjects without a diagnosis of ILD whose CT scans on radiology review showed significant interstitial lung disease with a prior history.

For this sub-study, a sample of 1,784 current or former smoking non-COPD subjects were included who had had their chest CT scans performed with a calcium calibration phantom [INTable^{TM} CT scanner pads (Image Analysis Inc., Columbia, Kentucky)] and were part of an earlier study of bone density. See Figure 1 for a detailed flow chart. This subset of subjects has been previously described [14].

CT scanning and assessment of DISH

The scans were acquired using multi-detector CT scanners and standardized protocols. Visual scoring for DISH was performed by trained imaging analysts using TeraRecon software and 3D sharp reconstructions from the stored image files. A minimum of two readers per scan scored scans as DISH if there were three or more adjacent levels of flowing osteophytes. Scans with divergent reads were adjudicated by a third reader. Typical flowing lesions with extensive disc narrowing were not scored as DISH. Additionally, the kyphotic angle was measured between Th1 and Th12 in the sagittal view and differences of more than 5 degrees between readers were adjudicated by a third reader.

CT measurement of the lungs

Quantitative CT measures have been described in detail previously and include the 15th percentile of low-attenuation areas (n=1,743) (Perc15, surrogate for emphysema), percentage of lung high attenuation areas between -250 and -600 HU (HAA) as a surrogate for interstitial lung abnormalities, percentage of gas trapping (n=1,575) (expiratory to inspiratory ratio of mean lung attenuation; E/I-ratio MLA), and airway wall thickness (n=1,737) (expressed as the square root of the wall area at a theoretical airway with an internal

perimeter of 10mm; Pi10) [15]. Furthermore, the total lung capacity (TLC) in inspiration on CT was quantified (n=1,743).

Spirometry and clinical assessment

All subjects completed pre- and post-bronchodilator (with albuterol) spirometry following ATS guidelines using the EasyOne spirometer (ndd, Andover MA). Studies have shown that spirometry with FVC and FEV1 can be used as a surrogate of restriction but do not define the etiology of restriction [11]. The estimated prevalence of RSP based on spirometry varies considerably due to variable definitions in the literature and the use of bronchodilation. A recent study investigated the impact of three different definitions of the so-called restrictive spirometric pattern (RSP) and the difference between pre- and post-bronchodilator spirometry on prevalence estimates [12]. The estimated prevalence in a general population differed most on the choice of pre- and post-bronchodilator spirometry.

Presence of a restrictive spirometric pattern (RSP) was defined as a fixed threshold of FVC< 80% predicted with a FEV_1/FVC ratio >/= 0.7 on post-bronchodilator spirometry [12]. Definite COPD subjects were excluded based on spirometry (FEV_1 < 80% predicted with an FEV_1/FVC < 0.7). The short-form (SF) 36 Health Survey (n=1,423), BODE index (Body mass index, airflow Obstruction, Dyspnea and Exercise capacity) (n=1,774), and St. George's Respiratory Questionnaire (SGRQ) (n=1,783) scores were, collected and calculated from the Phase 1 or research visit. A 6-minute walk test (6MWT) was performed at baseline (n=1,774) [16,17,18].

Statistical analysis

Normally distributed variables were stated as mean (standard deviation (SD)) and non-normal data as median (interquartile range (Q1-Q3)). Differences between DISH and no DISH and subjects with RSP or no RSP were compared using a Student's t-test (normal continuous variables) and a Mann-Whitney U test

(non-normal continuous variables) and a Chi square test (categorical variables). Multivariable logistic regression analysis using backward selection was performed to study the association of RSP with DISH adjusting for age, race, packyears, height, BMI, diabetes, high cholesterol, hypertension, HAA, Pi10, E/I-ratio and Perc15. Subjects were grouped by both DISH and RSP status to assess the impact these variables on quality of life and function. Comparisons were made across groups using ANOVA, with t tests between groups to define significant differences. A significance level of <0.05 was set. Statistical analyses were performed with SPSS version 25.0.0 (IBM Statistics, Chicago, Illinois, USA).

Results

Baseline characteristics

DISH was present in 236 subjects (13.2%). In subjects with DISH, RSP pulmonary function was significantly more prevalent than in those without DISH, 38.1% versus 19.4% (p<0.001). In **Table 1** characteristics by the presence or absence of DISH are given. DISH subjects were older and more likely to be male (69% male vs 47%). It was less common in African-Americans (28% AA with DISH vs 39% AA in no DISH subjects). DISH subjects were less likely to be current smokers (44% vs 61%) but had significantly higher BMI. Chest CT measures (Perc15 (emphysema), HAA (high attenuation area), Pi10 (airway wall thickening) and E/I MLA ratio (gas trapping) were not significantly different between subjects with DISH and no DISH, except that the kyphosis angle was greater in the DISH subjects (39.2 vs 35.1, p<0.001). Hypertension, high cholesterol and diabetes were significantly more present in patients with DISH.

see **Table 1**.

RSP pulmonary function was present in 391 subjects (21.9%) of the total group of 1784 subjects. The RSP subjects had significantly higher packyears of smoking (42.4 vs 36.9, p<0.001) and were slightly more likely to be current smokers (64% vs 58%, p=0.015). Details on the baseline characteristics stratified by RSP

pulmonary function and normal spirometry are shown in **Table 2**. BMI was significantly higher in the subjects with RSP, mean (SD) 32.1 (7.2) and 28.9 (5.7), p<0.001. There was no significant difference in kyphotic angle between the two groups, mean (SD) 35.0 (11.5) and 35.8 (10.4), p=0.180). Perc15 inspiration was significantly higher in the those with RSP pulmonary function, mean (SD) HU -887 (26) versus -908 (21) HU, p<0.001. The mean (SD) HAA was not different in those with RSP pulmonary function compared to the normal group; 3.9% (1.4) and 3.8% (1.4), p=0.703. The RSP pulmonary function group had a significantly higher Pi10 (bronchial wall thickening) compared to the normal group, mean (SD) 3.71 (0.13) versus 3.63 (0.11) mm, p<0.001. The E/I MLA ratio was comparable in both groups. The mean (SD) TLC on CT was significantly lower in those with RSP pulmonary function, 4.6 (1.1) and 5.5 (1.3), p<0.001.

Univariable and multivariable associations with the presence of RSP pulmonary function

Table 3 lists the outcomes of the univariable and multivariable logistic regression analysis of the presence of RSP. At univariable analysis subjects with DISH had a significantly higher odds ratio (OR) of having RSP, 2.55 (CI 95% 1.91 - 3.42), see **Table 3**. At multivariable logistic regression analysis, the presence of DISH remained significantly associated with RSP after adjusting for age, race, packyears, height, BMI, diabetes, hypertension, high cholesterol, HAA, Pi10, E/I-ratio and Perc15, OR 1.78 (CI 95% 1.22 – 2.60), p=0.003. Detailed results of the multivariable logistic regression are shown in **Table 3**.

Association between DISH, RSP and quality of life metrics, BODE and 6MWD

We assessed DISH alone compared to the groups with no DISH/no RSP and found that the effect of DISH was a significant reduction in six minute walk distance [1480 (351) feet for DISH alone vs 1560 (323) feet for No DISH/ No RSP, p= 0.003, and yet worse six minute walk distance for those with both DISH and RSP disease (**Table 4**). When combined with RSP the additional effect of DISH was a higher/better score for the SF-36 MCS score [50.5 (10.4) vs 46.5 (12.5), p= 0.009] than RSP alone. Similarly, the SGRQ Total score

was better (lower) in RSP subjects who also had DISH [26.4 (22.8) vs 31.6 (23.7), p =0.03]. The RSP groups both with and without DISH had significantly worse spirometry, dyspnea, SGRQ score, BODE and SF-36.

Discussion

We found, after correction for several known causes of restrictive lung function, that DISH was significantly associated with RSP in a cohort of current and former smokers excluding smokers with a low FEV1/FVC ratio. DISH is a common 'incidental finding' in imaging studies. Our findings contribute to the understanding of the association between DISH and pulmonary function abnormalities, and our data suggest that DISH may be a previously unrecognised cause of extrinsic restriction-like pulmonary function in subjects with a substantial smoking history.

In the last decade, multiple population-based studies have shown that a significant proportion of the general adult population has RSP or restriction-like pattern on spirometry [19,20]. In heavy smokers without prior known interstitial lung disease in the COPDGene cohort, a large portion of the subjects likely had this physiology as a result of small airway inflammatory disease. This is supported in our data by a significant increase in Pi10 in the RSP group. It is important to identify restrictive elements that may also contribute to this physiology. The common restrictive elements that contribute to RSP can be divided into intrinsic and extrinsic factors [7]. Intrinsic factors can be further split into interstitial, pleural and alveolar causes. In this study, we corrected for alveolar disease such as emphysema, and significant amounts of pleural fluid were not observed in these subjects. Our cohort excluded subjects with diagnosed interstitial lung disease and screened CT scans after enrollment for ILD. We further assessed for interstitial abnormalities by quantifying high attenuation areas of the lung. We found no differences in HAA in those with or without RSP and those

with or without DISH. Known extrinsic factors are obesity, ascites, neuromuscular diseases and kyphoscoliosis [20].

In our regression models, we corrected for two important extrinsic factors which may cause RSP: obesity (BMI) and kyphosis. There was no difference between the groups in kyphosis; however, we did not look into (kypho)scoliosis. It has been shown that long-term milder degrees of scoliosis can influence respiratory function and there can also be a role for rib ankylosis and deformities.[21] We do not expect scoliosis to be a major issue because previous studies have suggested that especially severe scoliosis (>60 degrees Cobb angle) has a substantial effecton lung function [22]. None of the included DISH participants had scoliosis of this severity and furthermore the Cobb angle was the same in the group with RSP compared to those with normal lung function. While we did not correct for neuromuscular disease, we do not think it can explain our observations in this cohort due to the low prevalence of neuromuscular disease in the general population (1-10 per 100,000) [23].

Our data suggest that DISH may create an extrinsic restrictive factor that contributes to RSP in heavy smokers without known interstitial lung disease. This pattern has been suggested in a previous study in which the thoracic cage is forcing individuals to ventilate by diaphragm contraction only eventually leading to restriction of pulmonary function [24]. A previous case report suggested that advanced DISH creates a rigid ‘thoracic cage’ due to the osseous bridging of vertebral bodies, ribs and sternum, reducing the mechanism of lung expansion to diaphragm contractions only [5]. Our findings support that an extra-thoracic cause has to be considered as an explanation for the DISH contribution to the RSP. DISH should also be included in the differential diagnosis of RSP, especially after the elimination of other common restrictive causes. Because a chest CT scan is often performed when restriction is diagnosed, it is possible

to specifically look for the presence of DISH. Our study suggests that DISH may impact thoracic cage mobility and we demonstrate a novel potential extrinsic factor for RSP spirometry in current and former smokers. RSP spirometry in smokers independent of DISH is strongly associated with more dyspnea, worse BODE index and lower walking distance consistent with a primary effect of the smoking-induced lung disease. The presence of DISH is shown to have an additional negative influence on walking distance in current and former smokers at high risk for progressive COPD.

RSP with and without DISH is associated with worse spirometry, more dyspnea, worse quality of life by SGRQ and SF-36, higher worse BODE scores and lower six minute walk distances in this group of current and former smokers without spirometric COPD. This may be related to small airways inflammation that is associated with early COPD in smokers. We identify DISH alone and in association with RSP pulmonary function, but the major impact of DISH appears to be a reduction in six minute walk distance in those subjects who have DISH alone without associated RSP pulmonary function. This suggests that the occurrence of DISH in combination with smoking-induced airway inflammatory disease causes a measurable decrease in functional performance (6 minute walk).

RSP has been shown to be associated with a decreased quality of life based on SGRQ scores [23] and a recent study including two large population-based cohorts of adults, showed that the presence of RSP significantly affects the physical health component of quality of life [25,26]. However, when DISH is associated with RSP, subjects have significantly better SGRQ Total score. This suggests that the impact of this extrinsic restriction on respiratory quality of life has less negative effect on symptoms other than exercise performance (six minute walk).

It has been hypothesized that DISH is associated with the metabolic syndrome. In our data we observed that both DISH and RSP are associated with higher BMI, more packyears, diabetes, hypertension and high cholesterol. Furthermore all the univariate odds ratio's were significant. After multivariable adjustment higher BMI and more smoking remained in the model, but also the association between RSP and DISH weakened but remained significant. This suggests that to some extent the association between DISH and RSP is direct as argued previously in the discussion. In cross-sectional studies care is needed with causal assumptions. We think our observation on the association between DISH and cardiometabolic factors support further causal studies into the relation between RSP, DISH and metabolic syndrome. [27,28]

Strengths of this study include the well-characterized cohort of smokers and the use of post-bronchodilator spirometry. To our knowledge this is the largest study examining DISH and its relation to RSP in current and former smokers. The study limitations include: First, selection criteria limit the cohort to heavy current or former smokers. Second, RSP in heavy smokers remains a complex mixture of subjects with progressive obstruction characterized as early stages of small airway disease and restriction from multiple etiologies.

The definition of RSP pulmonary function used in our study is the same as that commonly used to define restriction-like physiology in general population studies [12]. Other definitions could be considered (i.e. FVC < 80% & FEV_1/FVC > LLN (Lower Limit of Normal) and FVC < LLN & FEV_1/FVC > LLN) [12]. A recent study investigated the prevalence of a restrictive spirometric pattern (RSP) in a general population of 726 subjects in the age range 21-86 years by obtaining spirometry [12]. The prevalence of RSP was calculated according to three different definitions based on pre- as well as post-bronchodilator spirometry. The results of this study showed no significant difference between the three definitions of RSP. On the other hand, the use of pre- and post-bronchodilator showed more significant variation in terms of RSP [12].

In conclusion, we found that DISH is significantly associated with RSP in a cohort of heavy smokers. The association of DISH persisted after extensive correction for known intrinsic restrictive factors, supporting the hypothesis that DISH can potentially lead to a novel extrinsic cause of restrictive-like spirometry in a rigid thoracic cage. To some extent DISH and RSP maybe components of the metabolic syndrome.

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Table 1 – Baseline characteristics stratified by DISH and no DISH

DISH= Diffuse Idiopathic Skeletal Hyperostosis. BMI= Body Mass Index; Perc15= HU value at the 15th percentile (n=1,743); E/I MLA= expiratory to inspiratory ratio of mean lung attenuation (n=1,575); Pi10= square root of wall area of a 10-mm lumen perimeter (n=1,737); FEV1= Forced expiratory volume in 1 second; FVC=Forced Vital Capacity; HAA= High Attenuation Area, TLC= total lung capacity (n=1,743).

Variable	DISH[N=236]	No DISH [N=1548]	*P-value*
Restrictive- like pulmonary function (N), [%]	90 (38.1%)	301 (19.4%)	<0.001
Age (y), mean (SD)	61.8 (8.8)	55.9 (8.0)	<0.001
Gender [M/F]	164/72	731/817	<0.001
Race [White/Black] (N)	168/68	939/609	0.001
Packyears (py), mean (SD)	41.0 (23.4)	37.7 (20.6)	0.023
Current smoker [N] (%)	104 (44.1)	950 (61.4)	<0.001
Weight [Kg], mean (SD)	98.5 (19.5)	84.3 (18.8)	<0.001
Height [cm], mean (SD)	173 (9)	170 (10)	<0.001
BMI [kg/m^2], mean (SD)	33.0 (6.5)	29.0 (6.0)	<0.001
Diabetes present	62 (26.3%)	164 (10.6%)	<0.001
Hypertension present	132 (55.9%)	577 (37.3%)	<0.001
High cholesterol	118 (50%)	516 (33.3%)	<0.001
Perc15 Insp [HU], mean (SD)	-902.1 (23.9)	-901.4 (24.2)	0.664
HAA [%], mean [SD]	3.9 (1.6)	3.8 (1.3)	0.697
E/I MLA [%], mean (SD)	82.1 (4.7)	81.6 (5.2)	0.819
Pi10 [mm], mean (SD)	3.6 (0.12)	3.6 (0.12)	0.218
FEV_1 pp [%], mean (SD)	86.7 (16.0)	92.3 (15.4)	<0.001
FVC pp [%], mean (SD)	84.7 (15.2)	92.0 (15.0)	<0.001

FEV_1/FVC ratio	0.78 (0.05)	0.78 (0.05)	0.592
TLC on CT [Ltr]	5.5 (1.3)	5.3 (1.3)	0.027
Kyphotic Angle, mean (SD)	39.2 (10.3)	35.1 (10.6)	<0.001

Table 2 – Baseline characteristics stratified by presence of RSP pulmonary function

DISH= Diffuse Idiopathic Skeletal Hyperostosis. BMI= Body Mass Index; Perc15= HU value at the 15th percentile (n=1,743); E/I MLA= expiratory to inspiratory ratio of mean lung attenuation (n=1,575); Pi10= square root of wall area of a 10-mm lumen perimeter (n=1,737); FEV1= Forced expiratory volume in 1 second; FVC=Forced Vital Capacity; HAA= High Attenuation Area, TLC= total lung capacity (n=1,743).

Variable	RSP pulmonary function [N=391]	Normal [N=1393]	*P-value*
DISH (N), [%]	90 (23.0%)	146 (10.5%)	<0.001
Age (y), mean (SD)	57.5 (8.6)	56.5 (8.3)	0.031
Gender [M/F]	201/190	694/699	0.310
Race [White/Black] (N)	233/158	874/519	0.140
Packyears (py), mean (SD)	42.4 (24.1)	36.9 (20.0)	<0.001
Current smoker [N] (%)	250 (63.9)	804 (57.7)	0.015
Weight [Kg], mean (SD)	94.1 (21.6)	84.0 (18.3)	<0.001
Height [cm], mean (SD)	171(10)	170 (10)	0.098
BMI [kg/m^2], mean (SD)	32.1 (7.2)	28.9 (5.7)	<0.001
Diabetes present	62 (26.3%)	164 (10.6%)	<0.001
Hypertension present	132 (55.9%)	577 (37.3%)	<0.001
High cholesterol	118 (50%)	516 (33.3%)	<0.001
Perc15 Insp [HU], mean (SD)	-887.0 (26.5)	-905.5 (21.8)	<0.001
HAA [%], mean [SD]	3.9 (1.4)	3.8 (1.4)	0.703
E/I MLA [%], mean (SD)	82.1 (5.4)	81.5 (5.0)	0.092
Pi10 [mm], mean (SD)	3.71 (0.13)	3.63 (0.11)	<0.001
FEV_1 pp [%], mean (SD)	72.4 (10.0)	96.9 (12.4)	<0.001
FVC pp [%], mean (SD)	71.0 (7.9)	96.7 (11.3)	<0.001
FEV_1/FVC ratio	0.79 (0.06)	0.78 (0.05)	0.001
TLC on CT [Ltr]	4.6 (1.1)	5.5 (1.3)	<0.001

Kyphotic Angle, mean(SD)	35.0 (11.5)	35.8 (10.4)	0.180

Table 3 – Association between RSP pulmonary function and DISH: results of the univariable and multivariable logistic regression analysis

Data given are from univariable and multivariable logistic regression analysis (backward conditional). DISH= Diffuse Idiopathic Skeletal Hyperostosis. BMI= Body Mass Index; Perc15= HU value at the 15th percentile (n=1,743); E/I MLA= expiratory to inspiratory ratio of mean lung attenuation (n=1,575); Pi10= square root of wall area of a 10-mm lumen perimeter (n=1,737); FEV1= Forced expiratory volume in 1 second; FVC=Forced Vital Capacity; HAA= High Attenuation Area, TLC= total lung capacity (n=1,743).

Variable	Increment or comparison	OR [95% CI]	*P-value*	OR [95% CI]	*P-value*
		Univariable logistic regression analysis		**Multivariable logistic regression analysis**	
DISH	Yes/No	2.55 [1.91 – 3.42]	<0.001	1.78 [1.22 – 2.60]	0.003
Age	+1 year	1.02 [1.00 – 1.03]	0.032	1.03 [1.01 – 1.05]	0.002
Gender	Male vs Female	1.01 [0.85 – 1.33]	0.579		
Race	White vs Black	1.14 [0.91 – 1.44]	0.257	1.56 [1.13 – 2.16]	0.007
Packyears	+1 pack year	1.01 [1.01 – 1.01]	<0.001	1.01 [1.00 – 1.01]	0.007
Smoking status	Current vs former	1.30 [1.03 – 1.64]	0.027		
Weight	+ 1 kg	1.03 [1.02 – 1.03]	<0.001		
Height	+ 1 cm	1.01 [1.00 – 1.02]	0.099	1.04 [1.02 – 1.05]	<0.001
BMI	+1 kg/m2	1.08 [1.06 – 1.10]	<0.001	1.05 [1.02 – 1.07]	<0.001
Diabetes	Present vs absent	2.30 [1.71 – 3.10]	<0.001		
Hypertension	Present vs absent	1.64 [1.30 – 2.05]	<0.001		
High cholesterol	Present vs absent	1.25 [1.00 – 1.58]	0.055		
Pi10	+ 0.1 mm	1.06 [1.05 – 1.08]	<0.001	1.05 [1.03 – 1.06]	<0.001
E/I MLA ratio	+ 1%	1.02 [1.00 – 1.05]	0.093	1.03 [1.00 – 1.06]	0.039

HAA	+ 1%	1.02 [0.94 – 1.10]	0.703		
Perc15	+1 HU	1.03 [1.03 – 1.04]	<0.001	1.03 [1.02 – 1.04]	<0.001
Kyphotic Angle	+1 degree	0.99 [0.98 – 1.00]	0.180		

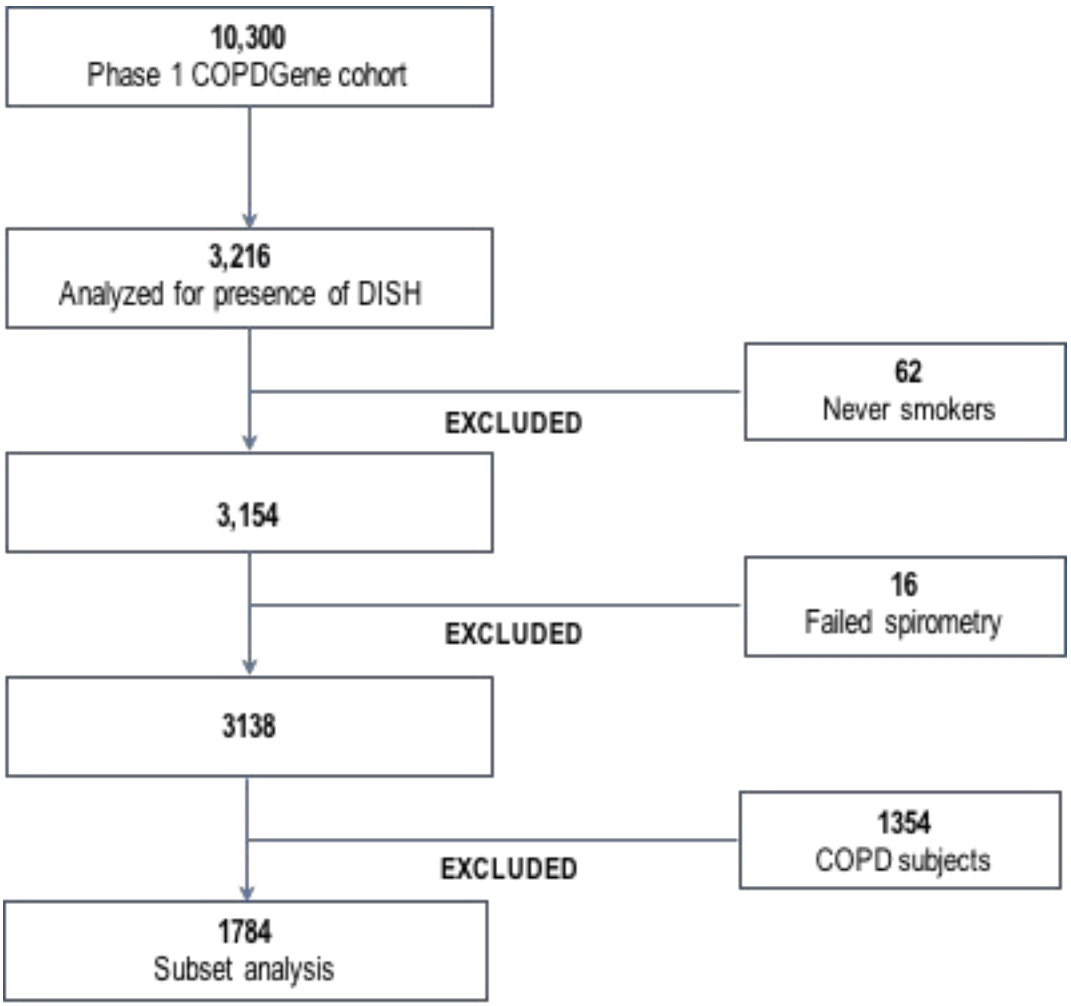
Table 4 – Association between both DISH status and presence or absence of RSP pulmonary function on quality of life and function

Subjects grouped by both DISH status and presence or absence of RSP pulmonary function to assess the impact of DISH and or RSP on quality of life and function. Comparisons were made across groups using ANOVA, with t tests between groups to define significant differences. SF-36 = short-form 36 health survey (n=1,423); BODE index = body mass index, airflow obstruction, dyspnea and exercise capacity) (n=1,774); SGRQ) = St. George's Respiratory Questionnaire (n=1,783); 6MWD = distance walked at 6-minute walk test (n=1,774).

	No Dish, No RSP pulmonary function	DISH + No RSP pulmonary function	RSP pulmonary function + No DISH	Both DISH and RSP pulmonary function
Number of subjects	1247	146	301	90
FEV_1 pp [%], mean (SD)	97.1 (12.4)	94.9 (12.7)	72.2 (9.7)*	73.3 (10.8)*
FVC pp [%, mean (SD)	97.1 (11.4)	93.2 (11.7)*	71.1 (7.8)*^	70.8 (8.5)*^
MMRC Dyspnea score, mean (SD)	0.8 (1.2)	0.8 (1.1)	1.5 (1.5)*^	1.3 (1.5)*^
SGRQ Total, mean (SD)	17.8 (19.0)	16.8 (17.4)	31.6 (23.7)*^	26.2 (22.8)*^"
SF-36 PCS, mean (SD)	48.0 (9.8)	47.8 (9.4)	42.1 (10.5)*^	42.6 (11.0)*
SF-36 MCS, mean (SD)	49.1 (11.3)	50.6 (11.3)	46.5 (12.5)*^	50.5 (10.4)"
BODE Score, mean (SD)	0.52 (0.93)	0.43 (0.84)	1.3 (1.4)*^	1.0 (1.4)*^
Six minute walk distance [feet], mean (SD)	1560 (323)^	1480 (351)	1326 (347)*^	1314 (390)*^

*= p<0.0001 for comparison to No DISH/No PRISm pulmonary function group
^ = p<0.001 for comparison to DISH/no PRISm pulmonary function
" = p<0.05 for comparison to PRISm pulmonary function/no DISH

Figure 1. Flow chart of subjects included in this analysis



Clinical Center	Institution Title	Protocol Number
National Jewish Health	National Jewish IRB	HS-1883a
Brigham and Women's Hospital	Partners Human Research Committee	2007-P-000554/2; BWH
Baylor College of Medicine	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22209
Michael E. DeBakey VAMC	Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals	H-22202
Columbia University Medical Center	Columbia University Medical Center IRB	IRB-AAAC9324
Duke University Medical Center	The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB)	Pro00004464
Johns Hopkins University	Johns Hopkins Medicine Institutional Review Boards (JHM IRB)	NA_00011524
Los Angeles Biomedical Research Institute	The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center	12756-01
Morehouse School of Medicine	Morehouse School of Medicine Institutional Review Board	07-1029
Temple University	Temple University Office for Human Subjects Protections Institutional Review Board	11369
University of Alabama at Birmingham	The University of Alabama at Birmingham Institutional Review Board for Human Use	FO70712014
University of California, San Diego	University of California, San Diego Human Research Protections Program	070876
University of Iowa	The University of Iowa Human Subjects Office	200710717
Ann Arbor VA	VA Ann Arbor Healthcare System IRB	PCC 2008-110732
University of Minnesota	University of Minnesota Research Subjects' Protection Programs (RSPP)	0801M24949
University of Pittsburgh	University of Pittsburgh Institutional Review Board	PRO07120059
University of Texas Health Sciences Center at San Antonio	UT Health Science Center San Antonio Institutional Review Board	HSC20070644H
Health Partners Research Foundation	Health Partners Research Foundation Institutional Review Board	07-127
University of Michigan	Medical School Institutional Review Board (IRBMED)	HUM00014973
Minneapolis VA Medical Center	Minneapolis VAMC IRB	4128-A

Fallon Clinic	Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan	1143